10. (Amended) The isolated antibody of claim 9, wherein said polyclonal antibody is selected from the group consisting of a crude polyclonal antibody and an affinity purified polyclonal antibody.

A2 cont

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-10 are in this case. Claims 1-10 have been rejected.

By this amendment, claims 1-10 have been amended.

Attached herewith is a marked up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with marks to show changes made".

Drawings

Formal drawings will be filed following the allowance of the application. PTO-948 form was not received attached to the Official action. Nevertheless, a petition to accept color drawings and photographs is enclosed herewith.

Specification

The specification has now been amended so as to update the status of the priority documents.

35 USC § 101

The Examiner has rejected claim 1-10 under 35 USC § 101 because the claimed invention is directed to non-statutory subject matter. Claims 1-10 have now been amended to overcome the Examiner's 35 USC § 101 rejections.

The Examiner has further rejected claims 1-10 under 35 USC § 101 because the claimed invention is not supported by either an asserted utility or a well established utility.

Claims 1-10 have now been limited to mammalian heparanase having at least 95 % similarity to SEQ ID NO:2, to thereby overcome the Examiner's rejections.

35 USC § 112, First Paragraph Rejections

The Examiner has rejected claims 1-10 under 35 USC § 112, first paragraph since the claimed invention is not supported by either a specific asserted utility or a well established utility, as containing subject matter that was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and further for lack of enablement.

Claims 1-10 have now been limited to mammalian heparanase having at least 95 % similarity to SEQ ID NO:2, to thereby overcome the Examiner's rejections.

35 USC § 102(b) Rejections – WO 91/19197

The Examiner has rejected claims 1-10 under 35 USC § 102(b) as being anticipated by WO 91/19197 (Nicolson et al.). The Examiner's rejections are respectfully traversed. Claims 1-10 have now been amended.

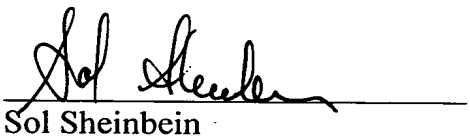
The antibody generated in the laboratory of Prof. Nicolson was first reported in the scientific literature by Jin et al. (Int J Cancer. 45(6):1088-95, 1990). This group isolated a 96 kDa mouse protein and used a peptide derived from the N-terminus of the partially purified protein to generate polyclonal as well as monoclonal antibodies. These antibodies detect a 96 kDa protein, which is obviously different from the mammalian heparanase which referred to in the application and which was later isolated from other tissues as currently reported by several groups. These antibodies were used by several research groups in collaboration with either one of the authors of the original paper (Marchetti et al. Cancer Res. 56(12):2856-63, 1996, Marchetti and Nicolson, Adv Enzyme Regul.37:111-34, 1997, Mollinedo et al. Biochem J. 327(3):917-23, 1997, copies are enclosed herewith). In 1994, Vouge et al (Int. J. Cancer 56:286-294, 1994, a copy is enclosed herewith) pointed out the fact that the antibodies claimed to detect heparanase actually detect GR94/endoplasmin, a previously cloned and characterized murine heat shock protein. The sequence and the molecular weight were in perfect agreement with those reported for the 96 kDa murine heparanase isolated by Nicolson's group. Later on, the mis-identification of the heparanase enzyme and consequently the antibodies generated against it was admitted and

accepted by the scientific community. The late papers (1996, 1997) still referring to these antibodies, as heparanase specific, are obscure. There is no doubt, however, that those antibodies do not recognize the heparanase identified by SEQ ID NO:2. Interestingly, Prof. Nicolson has abandoned heparanase research and does not take part in the major progress achieved during the recent years. Dr. Nakajima is a researcher at Novartis, a company that published recently the cloning of heparanase, with Nakajima as a last author (Toyoshima and Nakajima, J. Biol. Chem. 274(34):24153-24160, 1999, a copy is enclosed herewith). The published sequence is identical to SEQ ID NO:2 and the molecular weight of the purified protein is of 50 kDa.

It is hence clear that the WO 91/19197 publication fails to anticipate amended claims 1-10.

In view of the above amendments and remarks it is respectfully submitted that claims 1-10 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,



Sol Sheinbein
Attorney for Applicant
Registration No. 25,457

Date: 12 January 2002.

Encl.:
VERSION WITH MARKINGS TO SHOW CHANGES MADE; and
Jin et al., Int J Cancer. 45(6):1088-95, 1990;
Marchetti et al. Cancer Res. 56(12):2856-63, 1996
Marchetti and Nicolson, Adv Enzyme Regul.37:111-34, 1997
Mollinedo et al. Biochem J. 327(3):917-23, 1997
Vouge et al., Int. J. Cancer 56:286-294, 1994
Toyoshima and Nakajima, J. Biol. Chem. 274(34):24153-24160, 1999

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The paragraph starting on page 1, line 17, has now been amended as follows:

This is a continuation of U.S. Pat. application No. 09/322,977, filed June 1, 1999, which is a divisional of U.S. Pat. application No. 09/071,739, filed May 1, 1998, now U.S. Patent No. 6,177,545, issued January 23, 2001, which is a continuation-in-part of U.S. Pat. application No. 08/922,170, filed September 2, 1997, now U.S. Patent No. 5,968,822, issued October 19, 1999.

In the claims:

Claims 1-10 have now been amended as follows:

1. (Amended) An isolated antibody specifically binding at least one epitope of a mammalian heparanase protein, said heparanase protein being at least 95 % similar to SEQ ID NO:2.

2. (Amended) The isolated antibody of claim 1, wherein said heparanase protein is native.

3. (Amended) The isolated antibody of claim 1, wherein elicitation of the antibody is through *in vivo* or *in vitro* techniques, said antibody having been prepared by a process comprising the steps of:

(a) exposing cells capable of producing antibodies to said at least one epitope of said heparanase protein and thereby generating antibody producing cells;

(b) fusing said antibody producing cells with myeloma cells and thereby generating a plurality of hybridoma cells each producing monoclonal antibodies; and

(c) screening said plurality of monoclonal antibodies to identify a monoclonal antibody which specifically binds heparanase.

4. (Amended) The isolated antibody of claim 1, wherein the antibody is selected from the group consisting of a polyclonal antibody and a monoclonal antibody.

5. (Amended) The isolated antibody of claim 4, wherein said polyclonal antibody is selected from the group consisting of a crude polyclonal antibody and an affinity purified polyclonal antibody.

6. (Amended) An isolated antibody elicited by at least one epitope of a mammalian heparanase protein, said heparanase protein being at least 95 % similar to SEQ ID NO:2.

7. (Amended) The isolated antibody of claim 6, wherein said heparanase protein is recombinant.

8. (Amended) The isolated antibody of claim 6, wherein elicitation of the antibody is through *in vivo* or *in vitro* techniques, said antibody having been prepared by a process comprising the steps of:

(a) exposing cells capable of producing antibodies to said at least one epitope of said heparanase protein and thereby generating antibody producing cells;

(b) fusing said antibody producing cells with myeloma cells and thereby generating a plurality of hybridoma cells each producing monoclonal antibodies; and

(c) screening said plurality of monoclonal antibodies to identify a monoclonal antibody which specifically binds heparanase.

9. (Amended) The isolated antibody of claim 6, wherein the antibody is selected from the group consisting of a polyclonal antibody and a monoclonal antibody.

10. (Amended) The isolated antibody of claim 9, wherein said polyclonal antibody is selected from the group consisting of a crude polyclonal antibody and an affinity purified polyclonal antibody.